Human and veterinary pharmaceuticals regulation

Towards EU accession: Serbia's regulatory challenges, expectations and opportunities

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Republika Srbija
Ministarstvo zdravlja
Ministarstvo poljoprivrede, šumarstva i vodoprivrede,
Uprava za veterinu

Republic of Serbia
Ministry of Health
Ministry of Agriculture, Forestry and Water Management,
Veterinary Directorate

alims
Agencija za lekove i medicinska sredstva Srbije
Medicines and Medical Devices Agency of Serbia

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Overview of CVMP Activities on antimicrobial resistance

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anses
alimentation, environnement, travail

Outline

- BASIC LEGISLATION- COMM. DIRECTIVE 2009/9/EC*
- GUIDELINES
- SCIENTIFIC ADVISORY GROUP ON ANTIMICROBIALS (SAGAM)
- MONITORING

Basic legislation- Comm. Directive 2009/9/EC*

- **PART 3: SAFETY AND RESIDUES TESTS (safety test/other requirements)**
- **PART 4: PRE-CLINICAL AND CLINICAL TRIAL (preclinical)**

Basic legislation- Comm. Directive 2009/9/EC*

PART 3: SAFETY AND RESIDUES TESTS (safety test/other requirements)

4.2. Microbiological properties of residues

4.2.1. Potential effects on the human gut flora

The potential microbiological risk presented by residues of antimicrobial compounds for the human intestinal flora shall be investigated in accordance with established guidance.

4.2.2. Potential effects on the microorganisms used for industrial food processing

In certain cases, it may be necessary to carry out tests to determine whether microbiologically active residues may interfere in technological processes in the industrial processing of foodstuff.

Basic legislation- Comm. Directive 2009/9/EC

Safety

4.4. Development of resistance

Data on the potential emergence of resistant bacteria of relevance for human health are necessary in the case of veterinary medicinal products. The mechanism of the development of such resistance is particularly important in this regard. Where necessary, measures to limit resistance development from the intended use of the veterinary medicinal product shall be proposed.

Resistance relevant for clinical use of the product shall be addressed in accordance with Part 4. Where relevant, cross reference shall be made to the data set out in Part 4.

Basic legislation- Comm. Directive 2009/9/EC

PART 4: PRE-CLINICAL AND CLINICAL TRIAL (preclinical)

A.2. Development of resistance

Where relevant, data on the potential emergence of resistant organisms of clinical relevance are necessary for veterinary medicinal products. The mechanism of the development of such resistance is particularly important in this regard.

Measures to limit resistance development from the intended use of the veterinary medicinal product shall be proposed by the applicant.

Where relevant, cross reference shall be made to data set out in Part 3.

Guidelines

- VICH GL27: PRE-APPROVAL INFORMATION FOR REGISTRATION OF NEW VETERINARY MEDICINAL PRODUCTS FOR FOOD PRODUCING ANIMALS WITH RESPECT TO ANTIMICROBIAL RESISTANCE
- EFFICACY
- SUMMARY OF PRODUCT CHARACTERISTICS

VICH GL27 -Scope

VICH GL27: PRE-APPROVAL INFORMATION FOR REGISTRATION OF NEW VETERINARY MEDICINAL PRODUCTS FOR FOOD PRODUCING ANIMALS WITH RESPECT TO ANTIMICROBIAL RESISTANCE

- Applicable to all new applications containing new active ingredients or existing substances.
- Where new applications relate to existing substances, then a flexible approach is called for and it is likely that only basic information will be required.

VICH GL27 -Scope

- Not applicable to essentially similar products either by informed consent or by expiration of data protection i.e. the guideline shall not apply to Marketing Authorisations granted in accordance with Article 13 (1) (a) (i or iii) of Directive 2001/82/EC.

- **Applicable** to extensions and variations of existing products where an **increase of exposure of gut flora** to the antimicrobials in question **is anticipated.** Exceptions to this requirement would have to be supported by an adequate and scientifically sound justification.

- The guideline will not be applicable at renewals.

Guideline - VICH GL27

1. Basic information
    - 1.1 Antimicrobial class
    - 1.2 Mechanism and type of antimicrobial action
    - 1.3 Antimicrobial spectrum of activity
        - 1.3.1 General data
        - 1.3.2 MICs of target animal pathogens and (1.3.3) of food-borne pathogens and commensal organisms
            - Food-borne pathogens: *Salmonella enterica/ Campylobacter* spp.
            - Food-borne commensal organisms such as: *Escherichia coli/ Enterococcus* spp.

Guideline - VICH GL27

1. Basic information (cont.)
    - 1.4 Antimicrobial resistance mechanisms and genetics
    - 1.5 Occurrence and rate of transfer of antimicrobial resistance genes
    - 1.6 Cross-resistance and 1.7 Co-resistance
    - 1.8 Pharmacokinetic data
2. Additional information
    - 2.1 *In vitro* mutation frequency studies
    - 2.2 Antimicrobial agent activity in intestinal tract
    - 2.3 Other animal studies
    - 2.4 Supporting information
3. Discussion

Guidelines - Efficacy

Pharmacology;

- Antimicrobial class/ Mode and mechanism of action
- Antimicrobial spectrum of activity
- MIC and MBC
- Kinetics of bacterial killing/Post antibiotic effect
- PK-PD analysis

Demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/01).

Guidelines - Efficacy

Resistance

- Resistance mechanisms / Breakpoints

Clinical studies

- General studies/ Dose determination/Dose confirmation studies

Field trials

Demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/01).

Guidelines – SPC Antimicrobials

- "The <antimicrobial> should be used for treatment of severe infections only.
- "The <antimicrobial> should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.
- "Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.

Guidelines – SPC Antimicrobials

- "Due to the likely variability (time, geographical) in the occurrence of resistance of bacteria for <antimicrobial>, bacteriological sampling and susceptibility testing are recommended."
- "Whenever possible, the <antimicrobial> should only be used based on susceptibility testing"
- "Official, national and regional antimicrobial policies should be taken into account when the product is used."

Guidelines – SPC Antimicrobials

- "Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the <antimicrobial> and may decrease the effectiveness of treatment with<the following antimicrobial(s) or classes of antimicrobials>, due to the potential for cross-resistance."

SAGAM
SCIENTIFIC ADVISORY GROUP ON ANTIMICROBIALS

MANDATE

The Scientific Advisory Group is established to provide advice to the CVMP on all issues relating to antimicrobials.

- Keeping the CVMP abreast of developments at European and International level on the latest scientific knowledge with regard to all developments concerning the use of antimicrobials and in particular resistance development.
- Provide advice on the need to exercise certain control on those classes of compounds of greater importance to human medicine e.g. fluoroquinolones and 3rd and 4th generation cephalosporins.
- Consider recommendations for the CVMP on the type of communication and its content regarding relevant issues of authorisation requirements of antimicrobials.
- Support dossier evaluation for antimicrobials.
- International cooperation on antimicrobial related issues.
- Advice, through the CVMP, to European Commission on antimicrobial resistance related issues.
- Contribution to antimicrobial related workshops and training.

EMA / CVMP / SAGAM on going activities

- Macrolides
- Meticillin resistant *S. pseudintermedius*
- Considerations on companion animals and AMR
- Updating CVMP strategy on antimicrobials
- Considerations on benefit/risk for Marketing Authorisations for antimicrobials

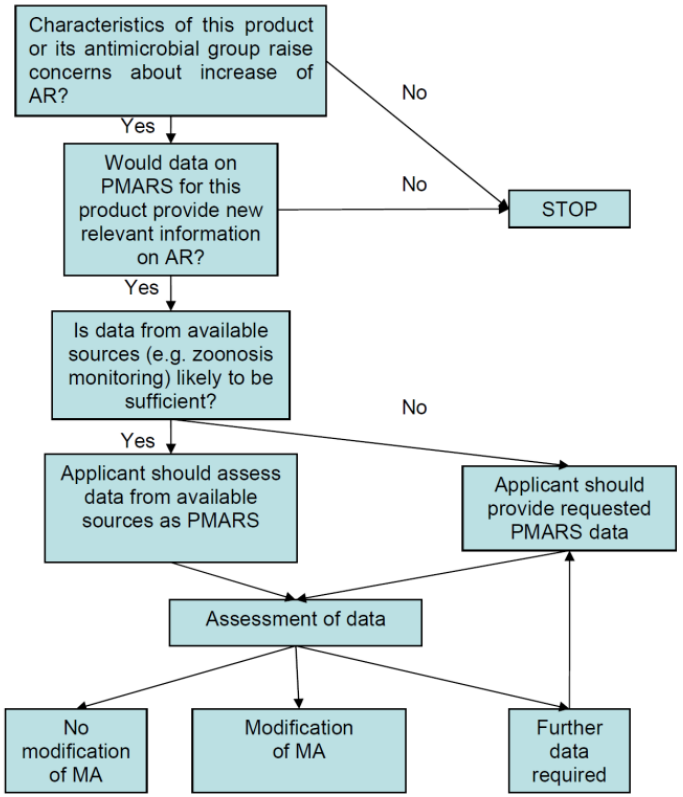
Most of CVMP recommendations require action by other stakeholders.

EMA/CVMP/SAGAM links to other institutions on AMR

- Collaboration with EFSA on ESC
- Input EU-US task force on AMR
- Input Codex Task Force AMR
- Collaboration HMA strategic plan on antimicrobial issues
- Joint Opinion on AMR focused on zoonotic infections (ECDC, EFSA, SCENIHR and EMA)
- Joint scientific report of ECDC, EFSA and EMA on MRSA

MONITORING

AMR Surveillance as Post-Marketing Authorisation Commitment



Reflection Paper on Antimicrobial Resistance Surveillance as Post-Marketing Authorisation Commitment (EMEA/CVMP/SAGAM/428938/07)

European Surveillance of Veterinary Antimicrobial Consumption - ESVAC

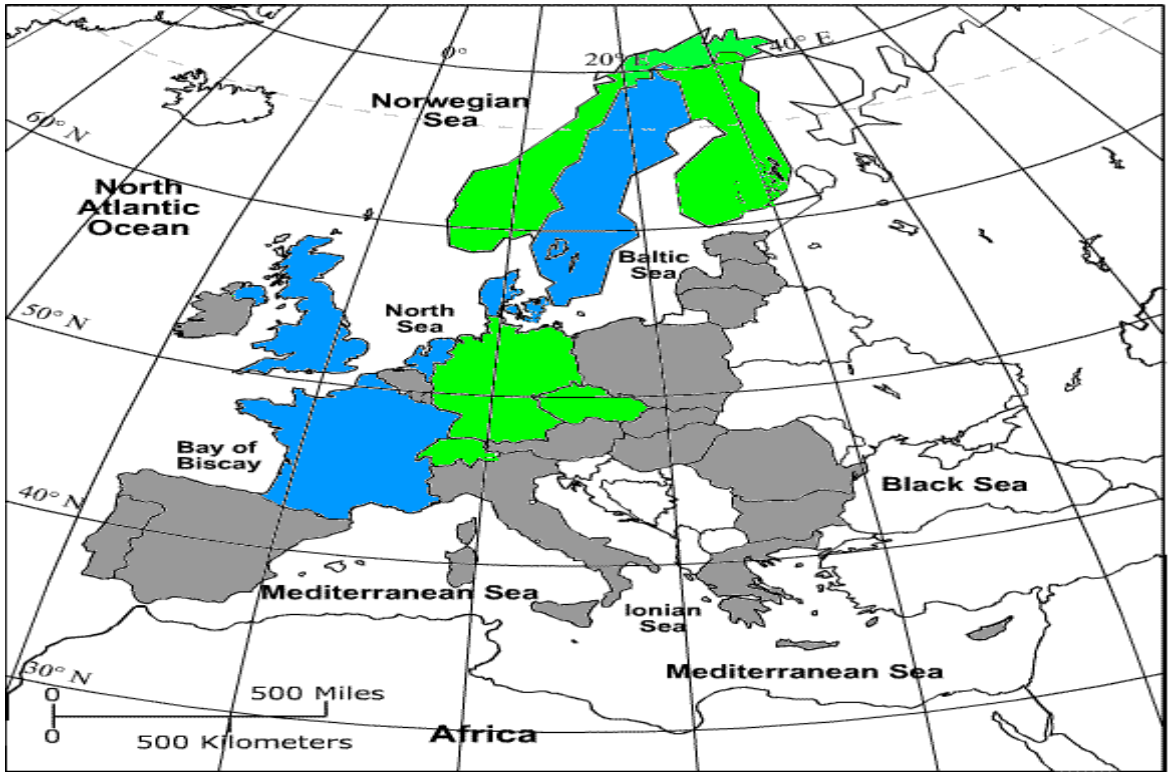
Monitoring of consumption of veterinary antimicrobials

European Guidelines/Training

Collect each year of drugs sales by member states authorities

Data analysed according national animal production

"State of the art" before the ESVAC project was initiated



10 countries (8 MS)

5 collect per species

Coverage of > 50 % (slaughtered) biomass in MS

ESVAC project plan - revised

ESVAC I. Pilot project (2009-2011)

ESVAC II. Operational Phase: Collating overall sales data from all Member States (2012-onwards) and on estimations per species

ESVAC III. Collating data on overall sales, estimates per species and on actual usage of antimicrobials by animal species, production category, indication etc (2013-onwards)

CONCLUSION

Antimicrobial resistance is a complex issue

Several activities performed by EMA/CVMP/SAGAM in close collaboration with EFSA, ECDC, Commission and international bodies (WHO/FAO/OIE)

Awareness of prescribors is essential.

Prudent use is the only way to preserve a sustainable efficacy of antimicrobials

Thanks for your attention

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